HOW TO TIE REGULATORY REQUIREMENTS TO ANALYTICAL CHEMISTRY WORLD

Ying Verdi
IVT LAB WEEK EUROPE
June 2017

UPSHER-SMITH
Partners in Health Since 1919
Disclaimer:

I am an analytical chemist, not a regulatory scientist
Desired State

A maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight.

- Janet Woodcock, Oct. 2005

Robust, innovative analytical science is the backbone assuring high quality drugs

Regulatory science is a scientific discipline consisting of the development and application of scientific methods, tools, approaches, and other relevant processes derived from various scientific disciplines used to support regulatory and other policy objectives.

Regulatory science is the application of the scientific method to improve the development, review, and oversight of new drugs, biologics, and devices that require regulatory approval prior to dissemination.
Outline

• Common Technical Document (CTD)
• Common deficiencies found on analytical activities
• Tips on analytical activity considerations for submission
Outline

• Common Technical Document (CTD)
• Common deficiencies found on analytical activities
• Tips on analytical activity considerations for submission
Common Technical Document (CTD)

- Background on ICH process and CTD
- Overview of eCTD format and granularity
- Key ICH References
ICH - International Council for Harmonisation

• Started in 1990

• Mission: to achieve greater harmonisation worldwide to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner

• Includes US, EU and Japan founding regulatory members
ICH Working Groups

• Q for Quality
  Chemistry, Manufacturing and Controls (CMC)

• S for Safety
  Non-clinical Studies

• E for Efficacy
  Clinical Studies (Human Subjects/Patients)

• M for Multi-Disciplinary
  Common Technical Document (CTD)
Key ICH References for Analytical Chemist

- M4Q(R1)  CTD – Quality (Module 2.3 QOS and Module 3)  Sep. 2002
- Q1A(R2)  Stability  Feb. 2003
- Q1B  Photostability  Nov. 1996
- Q1D  Bracketing and Matrixing Designs  Feb. 2002
- Q1E  Evaluation of Stability Data  Feb. 2003
- Q2(R1)  Validation of Analytical Procedures  Nov. 2005
- Q3A(R2)  Impurities in DS  Oct. 2006
- Q3B(R2)  Impurities in DP  Jun. 2006
- Q3C(R6)  Residual Solvents  Nov. 2016
- Q3D  Elemental Impurities  Dec. 2014
- Q6A  Specification  Oct. 1999
ICH: 5-Step Guidance Process

Step 1  Consensus Building: Expert Working Group endorsement
Step 2  Start of Regulatory Action: ICH recommends adoption
Step 3  Regulatory Consultation: Published in Federal Register
Step 4  Guidance is finalized
Step 5  Implemented according to the regulations of individual areas

Revisions
> 70 guidance to date
CTD Organization

Module 1:Regional Information
Module 2:Summaries
Module 3:Quality
Module 4:Safety
Module 5:Efficacy
CTD Module 2 (Summaries)

2.1 Common Technical Document Table of Contents (Modules 2-5)
2.2 CTD Introduction
2.3 Quality Overall Summary (QOS)
2.4 Nonclinical Overview
2.5 Clinical Overview
2.6 Nonclinical Written and Tabulated Summaries
2.7 Clinical Summary
CTD Module 3: Quality (CMC)

3.1 Table of Contents of Module 3
3.2 Body of Data
  3.2.S Drug Substance
  3.2.P Drug Product
  3.2.A Appendices
  3.2.R Regional Information (pertains to CMC)
3.3 Literature References
## Module 3 – Comparison of S and P Sections

<table>
<thead>
<tr>
<th>3.2.S Drug Substance</th>
<th>3.2.P Drug Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.2.S.1 General Information</td>
<td>3.2.P.1 Description and Composition of the Drug Product</td>
</tr>
<tr>
<td>3.2.S.2 Manufacture</td>
<td>3.2.P.2 Pharmaceutical Development</td>
</tr>
<tr>
<td>3.2.S.3 Characterisation</td>
<td>3.2.P.3 Manufacture</td>
</tr>
<tr>
<td><strong>3.2.S.4 Control of Drug Substance</strong></td>
<td>3.2.P.4 Control of Excipients</td>
</tr>
<tr>
<td>3.2.S.5 Reference Standards or Materials</td>
<td>3.2.P.5 Control of Drug Product</td>
</tr>
<tr>
<td>3.2.S.6 Container Closure System</td>
<td>3.2.P.6 Reference Standards or Materials</td>
</tr>
<tr>
<td>3.2.S.7 Stability</td>
<td>3.2.P.7 Container Closure System</td>
</tr>
<tr>
<td></td>
<td><strong>3.2.P.8 Stability</strong></td>
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## Granularity Comparison - Control

<table>
<thead>
<tr>
<th>3.2.S.4  Control of Drug Substance</th>
<th>3.2.P.4  Control of Excipients</th>
<th>3.2.P.5  Control of Drug Product</th>
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</thead>
<tbody>
<tr>
<td>3.2.S.4.1  Specification</td>
<td>3.2.P.4.1  Specification</td>
<td>3.2.P.5.1  Specification</td>
</tr>
<tr>
<td>3.2.S.4.2  Analytical Procedures</td>
<td>3.2.P.4.2  Analytical Procedures</td>
<td>3.2.P.5.2  Analytical Procedures</td>
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<td>3.2.S.4.3  Validation of Analytical Procedures</td>
<td>3.2.P.4.3  Validation of Analytical Procedures</td>
<td>3.2.P.5.3  Validation of Analytical Procedures</td>
</tr>
<tr>
<td>3.2.S.4.4  Batch Analyses</td>
<td>3.2.P.4.4  JOS</td>
<td>3.2.P.5.4  Batch Analyses</td>
</tr>
<tr>
<td>3.2.S.4.5  JOS</td>
<td>3.2.P.4.5  Excipients of Human or Animal Origin</td>
<td>3.2.P.5.5  Characterisation of Impurities</td>
</tr>
<tr>
<td></td>
<td>3.2.P.4.6  Novel Excipients</td>
<td>3.2.P.5.6  JOS</td>
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</table>
## Granularity Comparison - Stability

<table>
<thead>
<tr>
<th>3.2.S.7 Stability</th>
<th>3.2.P.8 Stability</th>
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</thead>
<tbody>
<tr>
<td>3.2.S.7.1 stability Summary and Conclusion</td>
<td>3.2.P.8.1 stability Summary and Conclusion</td>
</tr>
<tr>
<td>3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment</td>
<td>3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment</td>
</tr>
<tr>
<td>3.2.S.7.3 Stability Data</td>
<td>3.2.P.8.3 Stability Data</td>
</tr>
</tbody>
</table>
Filing Review Process

ANDA Submitted

Application Filing Review

Acceptable & Complete

YES

Quality Review  Labeling Review  Bioequivalence Review  Facility Inspection

NO

Refuse to Receive Letter
# Requirements for NDA vs ANDA

<table>
<thead>
<tr>
<th></th>
<th>NDA</th>
<th>ANDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemistry</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Manufacturing</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Testing</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Labeling</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inspections</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Animal Studies</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Clinical Studies</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bioavailability</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Bioequivalence</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Outline

• Common Technical Document (CTD)
• Common deficiencies found on analytical activities
• Tips on analytical activity considerations for submission
Common Deficiencies - Analytical Activities

- Examples of major and minor deficiencies
- Discussion on how to avoid common pitfalls
- Recommended best practices
<table>
<thead>
<tr>
<th></th>
<th>FY14 01OCT13 – 30SEP14</th>
<th>FY15 01OCT14 – 30SEP15</th>
<th>FY16 01OCT15 – 31MAR16</th>
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<tbody>
<tr>
<td># of RTRs</td>
<td>173</td>
<td>127</td>
<td>85</td>
</tr>
<tr>
<td># of Submissions</td>
<td>1473</td>
<td>539</td>
<td>474</td>
</tr>
<tr>
<td>%RTR</td>
<td>11.7%</td>
<td>23.6</td>
<td>17.9</td>
</tr>
</tbody>
</table>

- CDER-SBIA Regulatory Education for Industry (REdI), Generic Drugs Forum, April, 2016, Johnny Young
Common Major Deficiencies

• Unqualified impurity levels if toxicology studies are required for qualification
  - ICH Q3A and Q3B
  - ANDA Impurity Guidance
  - RTR Guidance on Lack of Justification of Impurity Limits

• New analytical methods are needed because method is not stability-indicating or is not sensitive enough, and significant method changes are necessary
  - FDA Guidance on Analytical Procedure and Method Validation
  - ICH Q3A and Q3B
Common Major Deficiencies

• Critical quality attributes are not identified or controlled
  • USP general chapters <1>, <2> (oral), <3> (topical and transdermal), <4>, and <5>
  • e.g. Particle Size Distribution (USP <429> Light Diffraction Measurement of Particle Size)

• Lack of comparative dissolution data per the drug specific guidance

• English translation

• Incomplete response
Common Deficiencies

• Lack of control on known degradation products
  • *Per other approved drug products, literature or scientific reports etc.*

• Lack of justification for proposed limits for identified and total impurities

• Analytical method for impurities is not properly validated
  • *RRT/RF/LOQ of each identified impurity should be provided.*
  • *Method validation should cover the appropriate range, e.g. lower limit, LOQ*
ICH Q2 and Q3 Guidance

Attachment 1: Thresholds for Degradation Products in New Drug Products

**Reporting Thresholds**

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Threshold[^2,^3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 1 g</td>
<td>0.1%</td>
</tr>
<tr>
<td>&gt; 1 g</td>
<td>0.05%</td>
</tr>
</tbody>
</table>

**Identification Thresholds**

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Threshold[^2,^3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1 mg</td>
<td>1.0% or 5 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>1 mg - 10 mg</td>
<td>0.5% or 20 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt;10 mg - 2 g</td>
<td>0.2% or 2 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g</td>
<td>0.10%</td>
</tr>
</tbody>
</table>

**Qualification Thresholds**

<table>
<thead>
<tr>
<th>Maximum Daily Dose</th>
<th>Threshold[^2,^3]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 10 mg</td>
<td>1.0% or 50 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>10 mg - 100 mg</td>
<td>0.5% or 200 µg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt;100 mg - 2 g</td>
<td>0.2% or 3 mg TDI, whichever is lower</td>
</tr>
<tr>
<td>&gt; 2 g</td>
<td>0.15%</td>
</tr>
</tbody>
</table>

Range - for the determination of an impurity: from the reporting level of an impurity to 120% of the specification

- Accuracy, Linearity, LOQ...

[^2]: TDI: Total Daily Intake
[^3]: This table assumes a person weighing 70 kg.
Example: Cozaar®
(Losartan Potassium Tablets)

- Maximum Daily Dose: 100mg
- 2 known degradation products per USP: 1H-Dimer and 2H-Dimer

<table>
<thead>
<tr>
<th>Acceptance Criteria</th>
<th>Known Degradation Product</th>
<th>Unknown Degradation Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>USP Monograph</td>
<td>0.5%</td>
<td>NA</td>
</tr>
<tr>
<td>ICH Q3(B)</td>
<td>200 μg TDI (0.2%)</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

- Impurity method validation range (min coverage): 0.1% - 0.6%
- QL: ≤ 0.1%
Common Deficiencies

• Failure to provide sufficient information on impurity reference standard

• Inadequate ID testing
  • Single or non-discriminative ID tests

• Lack of justification for exclusion of microbial limit tests
  • Susceptible to microbial contamination due to intrinsic hygroscopicity of DP, moisture content, manufacturing process-wet granulation, etc.
  • *USP general chapter <1111>, Microbiological examination of nonsterile product*
  • *USP general chapter <1112>, Application of water activity determination to nonsterile pharmaceutical products*
  • *ICH Q6A, Decision Tree #6*
Common Deficiencies

- Lack of testing on split tablets
  - Tablet scoring guidance

- Failure to provide justification for observed TRENDS (decreasing dissolution, increasing degradants, etc.)
  - Lack of root cause analysis and/or risk mitigation strategy for such trends
Outline

• Common Technical Document (CTD)
• Common deficiencies found on analytical activities
• Tips on analytical activity considerations for submission
Tips on Analytical Activity Considerations for Submission

- Specification and Justification of specification
- Method development, validation/verification, and transfer
- In-process and release testing
- Stability study and other one-off studies
- Analytical activity considerations for post-market changes
• To assure the product conforms to the critical quality attributes

• Specification must be established according to ICH guidelines, appropriate USP chapters and monographs, and from information gathered during development
Specification

• Specific Compendial Monograph
• USP General Chapters for DP Quality Tests
  • Chapter <1>: Injections and Implanted
  • Chapter <2>: Oral
  • Chapter <3>: Topical and Transdermal
  • Chapter <4>: Mucosal
  • Chapter <5>: OINDP
• ICH Q6A Decision Tree:
  • # 1 – Specified Impurity in DS
  • # 2 – Degradation Product in DP
  • # 3 – Particle Size
  • # 4 – Polymorphism in DS and DP
  • # 5 – ID, Assay, and Enantiomeric Impurity for Chiral DS and DP
  • # 6 – Micro for DS and Excipients
  • # 7 – Dissolution
  • # 8 – Micro non-sterile DP
Justification of Specification (JOS)

- Exclusion of a test must be justified
  - Normally performed for a type of drug product
  - Recommended in FDA guidance
  - Reported in other sections of the application, such as 3.2.P.5.4

- Justification for exclusion of expected impurities (in 3.2.S.3.2 or 3.2.P.5.5) is required

- For analytical method does not normally require justification, the appropriateness for the method must be supported by the information included in 3.2.P.5.2 and 3.2.P.5.3
Justification of Specification (JOS)

• Use data from the clinical efficacy, safety, bioavailability, and bioequivalence batches relevant development batches, primary stability batches, and PV batches, if available

• Use data from multiple manufacturing sites, if applicable

• Separate justification needed for release and shelf-life, if different

• Periodic or skip testing for a particular test requires justification
• Justification is to be provided for all acceptance criteria for each test included in the specification

• The justification of acceptance criteria should include the basis of the proposed limits, i.e. which batches were used to support the limits

• Statistical approaches that are used to establish the acceptance criteria are to be described
Analytical Method

- For compendial items, the USP test method is considered to be the regulatory method by FDA
  - FDA uses the compendial method when assessing if a product is in compliance with the USP

- Alternate method (equivalent or superior to USP method) is allowed

- Alternate method to USP method comparison is a must
  - FDA RTR Guidance

- List both the alternate method and USP method in the proposed spec
• MDVVT = Method Development Validation Verification Transfer
• Follow the guidance:
  • ICH Q2(R1)
  • FDA Guidance Analytical Procedure and Validation (Jul 2015)
  • FDA RTR Guidance (Dec 2016)
  • FDA SUPAC-SS (IVRT)
  • Two FDA Disso guidance on IR and MR (1997)
• USP General Chapters:
  • USP <1092> Disso method development and validation
  • USP <429> Light Diffraction Measurement of Particle Size
  • USP <1224>, <1225>, <1226>
Current Approach: Dissolution Testing

ANDA/sANDA

USP dissolution method available

Yes: Explore the USP method

No: FDA database dissolution method available

Yes: Explore the FDA recommended method

No: Develop a new dissolution method and provide to FDA the dissolution method development report

Method not appropriate for generic drug product

FDA Dissolution Method: http://www.accessdata.fda.gov/scripts/cder/dissolution/

- Dr. Banu S. Zolnik, SBIA REdI Generic Drug Forum 2017, Silver Spring, MD
In-process and Release Testing

• Work with the Regulatory representative to determine which batches to report in the application
  • Batches: clinical (NDA), bioequivalence (ANDA), safety (NDA), stability, and commercial, if applicable
  • Include any results from tests that are not part of the proposed specification.
  • Provide a link to the discussion regarding use of these methods in 3.2.P.2

• International Society for Pharmaceutical Engineering (ISPE)
  • BU/CU Tool
• Use 2 API lots (minimum) to manufacture 3 exhibit batches
  • For each strength across 3 exhibit batches, not 2 lots per batch
  • June 2013 FDA stability guidance and the Q&A guidance

<table>
<thead>
<tr>
<th>Strength</th>
<th>Exhibit Batch 1</th>
<th>Exhibit Batch 2</th>
<th>Exhibit Batch 3</th>
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</thead>
<tbody>
<tr>
<td>Strength X</td>
<td>API Lot 1</td>
<td>API Lot 1</td>
<td>API Lot 2</td>
</tr>
<tr>
<td>Strength Y</td>
<td>API Lot 1</td>
<td>API Lot 1</td>
<td>API Lot 2</td>
</tr>
<tr>
<td>Strength Z</td>
<td>API Lot 1</td>
<td>API Lot 1</td>
<td>API Lot 2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Strength</th>
<th>Exhibit Batch 1</th>
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<th>Exhibit Batch 3</th>
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</thead>
<tbody>
<tr>
<td>Strength X</td>
<td>API Lot 1</td>
<td>API Lot 1</td>
<td>API Lot 1</td>
</tr>
<tr>
<td>Strength Y</td>
<td>API Lot 1</td>
<td>API Lot 1</td>
<td>API Lot 1</td>
</tr>
<tr>
<td>Strength Z</td>
<td>API Lot 2</td>
<td>API Lot 2</td>
<td>API Lot 2</td>
</tr>
</tbody>
</table>
Stability

• Adhere to the guidance recommendations (stability, Q&A, and RTR)

• In case of failing accelerated conditions
  • Test intermediate condition sample
  • Submit 6-month worth of the 12 month study in the application
  • Do not stop the ACC study
  • Include 6-month data on the ACC condition

  6  6  6  3

• Storage Orientation
  • Liquid and semi-solid dosage forms
Other Studies – 3.2.P.8.1

- Provide a description of all other stability studies conducted on the drug product.
  - Photostability
  - Freeze-thaw
  - Forced degradation
  - In-use stability
  - Other studies that would support the proposed shelf-life and storage condition

- Include a description of the batches tested, exposure/conditions for the samples and testing conducted
Risk-based Reporting Categories

Minor Changes
• Annual Report

Moderate Changes
• CBE-0
• CBE-30

Major Changes
• PAS

Increasing Risk Adverse Effect
Common Post-market Changes

- Manufacturing Sites
- Manufacturing Process
- Components and Composition
- Specifications
  - Test
  - Acceptance Criteria
- Container Closure System
- Miscellaneous
  - Changes in the approved stability protocol
  - Change in the expiration date

Note: For multiple related changes, most restrictive reporting category will apply
Post-market Changes – Example on Spec Changes

- **PAS:**
  - Relaxing an acceptance criterion
  - Deleting any part of a spec
  - Establishing a new regulatory analytical procedure

- **CBE 30:** Relaxing an acceptance criterion or deleting a test to comply with an official compendium

- **CBE 0:** An addition to a spec

- **Annual Report:** Tightening of acceptance criteria

- **FDA Guidance** – [Changes to an Approved NDA or ANDA (April 2004)](https://www.fda.gov)
Conclusion

Let science guide the drug product development but follow the regulations.

There is a balance between regulatory science and analytical chemistry.

Most Importantly, always check with your regulatory affair colleague.

Work with the regulatory agencies and use data to tell your story.
References
FDA Resources

• **ANDA Filing Checklist**

• **Impurity Tables**

• **Other Information**
  • [SBIA](#) Program (CDER Small Business & Industry Assistance)
Stability and Method Validation

Stability

• Guidance – ANDAs: Stability Testing of Drug Substances and Products (Jun 2013)
• Guidance - Q1A(R2) Stability Testing of New Drug Substances and Products (Nov. 2003)
• ICH Q1

Method Validation

• MAPP 5310.7 Acceptability of Standards from Alternative Compendia (BP/EP/JP)
• Guidance - Analytical Procedures and Methods Validation for Drugs and Biologics (Jul 2015)
• ICH Q2(R1)
Impurity Guidance

- Guidance - Q3A Impurities in New Drug Substances (Jun 2008)
- Guidance - Q3B(R2) Impurities in New Drug Products (Jul 2006)
- Guidance - ANDAs: Impurities in Drug Substances (Jun 2009)
- Guidance - ANDAs: Impurities in Drug Products (Nov. 2010)
- Q3C Impurities: Residual Solvents
- MAPP 5015.8 Acceptance Criteria for Residual Solvents
- Guidance - Residual Solvents in Drug Products Marketed in the United States (Nov. 2009)
- Draft Guidance - Elemental Impurities in Drug Products (Jun 2016)
Dissolution Guidance

• Draft Guidance - Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (Dec. 2013)
  • BCS Classification System
  • Comparative disso requirement (when a compound specific guidance is unavailable)
  • Disso method development requirement to be included in the submission

• Draft Guidance - Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System (May 2015)

• Draft Guidance - Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs (Aug. 2015)


• Guidance – SUPAC-SS (May 1997)

• Guidance – SUPAC-IR (Nov. 1995)
Misc Guidance

• Guidance - Tablet Scoring: Nomenclature, Labeling, and Data for Evaluation (Mar. 2013)
• Guidance - Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs (Dec. 2000)
• Guidance - ANDAs: Pharmaceutical Solid Polymorphism (Jul 2007)
• MAPP 5015.10 Chemistry Review of Question-based Review (QbR) Submissions
• Draft Guidance - Comparability Protocols for Human Drugs and Biologics: CMC Information (Apr. 2016)
• ICH Q6A
• ICH M4Q